63. (Amended) The plant cell of claim 53 wherein the plant cell is from a dicotyledonous plant.

64. (Amended) The plant cell of claim 53 wherein the plant cell is from a monocotyledenous plant.

65. (Amended) The plant cell of claim 53 wherein the plant cell is from an alga.

REMARKS

The present invention stems from Applicants pioneering discovery that fully assembled antigen-specific immunoglobulin can be produced in a plant cell. Plant produced antibodies are useful for systemic protection through administration i.v. as well as localized protection through local administration to a mucosal surface (e.g., lungs, digestive tract, nasopharyngeal cavity, the urogenital system).

After amending the claims as set forth above, claims 53-65 and 67-76 will be pending in this application. The amendments and the new claims find ample basis in the application as filed and, therefore, raise no issue of new matter. For example, support for "antigen-specific immunoglobulin" is found, for example, at page 10, line 27-33 (emphasis added):

> Immunoglobulin product: A polypeptide, protein or multimeric protein **containing at least the immunologically active portion of an immunoglobulin heavy chain and is thus capable of specifically combining with an antigen**. Exemplary immunoglobulin products are an immunoglobulin heavy chain, immunoglobulin molecules, substantially intact immunoglobulin molecules, any portion of an immunoglobulin that contains the paratope, including those portions known in the art as Fab fragments, Fab' fragment, $F(ab')_2$ fragment and Fv fragment.

Support for "at least the portion of a variable region" finds basis throughout the specification. Indeed reference in the above quote to "at least the immunologically active portion" . . . any portion of an immunoglobulin . . . including those portions known in the art" strongly supports that a variety of fragments of the light or heavy chain were

contemplated that include the antigen binding or variable region, not just those forms of immunoglobulin known by proteolytic cleavage. This view is additionally supported by page 3, lines 1-6 (emphasis added) of the specification.

> One of the most useful aspects of using a recombinant expression system for antibody production is the ease with which the antibody can be tailored by molecular engineering. **This allows the production of antibody fragments and single-chain molecules, as well as the manipulation of full-length antibodies**. For example, a side [sic] range of functional recombinant-antibody fragments, such as Fab, F_v, single-chain and single-domain antibodies, may be generated.

This passage indicates that recombinant expression makes possible the production of a variety of antigen-specific immunoglobulins including those known from proteolytic processing (e.g., Fab) and those known only by recombinant expression of light and heavy chain variable regions (e.g., single chain antibodies).

FORMAL DRAWINGS

Formal drawings will be provided when allowable subject matter has been indicated.

CONTINUING DATA REFERENCE IN SPECIFICATION

The specification has been amended to reflect the continuing data on the face of the file.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The rejection of claims 53-66 as allegedly lacking a written description is respectfully traversed. The only basis that appears to be given for this rejection is the statement which alleges that "structural and physical features of the claimed plant cells cannot be ascertained in the absence of information about the specific functional activities of the nucleotide sequences they comprise." The examiner also cites to the decision in

University of California v Eli Lilly 119, F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) for support (hereinafter *"Eli Lilly"*).

First, it is respectfully submitted that the Federal Circuit decision in *Eli Lilly* does not support the rejection as alleged. The issue in *Eli Lilly* was whether the rat insulin gene, which was cloned in disclosed in the patent application, provided a written description for other insulin genes such as the human insulin gene, claimed in the resulting patent (the '525 patent). *Id.* at 1566. The Federal Circuit held in *Eli Lilly* that claims in the '525 patent to a nucleic acid genus were invalid because adequately describing a cDNA in a patent specification "requires the kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." *Id.* at 1569 (citing Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993)). The Federal Circuit rejected the argument of UC's counsel that the disclosure contained sufficient written description of the human insulin cDNA because the examples in the disclosure described how to isolate the cDNA from cells of a human. *Id.* at 1567.

Setting aside the issue of whether *Eli Lilly* is good law, the relevant facts in the present circumstances, however, are very much different from those in *Eli Lilly*. First, immunoglobulins are one of the most widely studied and well known proteins, due in part to their medical and commercial value, and a vast wealth of knowledge has been generated about their structure and function. For example, page 28 of the patent application refers to this information by citing to publications describing various immunoglobulin structures (lines 9-13), and a publication containing extensive amino acid and nucleic acid sequences for immunoglobulins (lines 19-22; Kabat et al, "Sequence of Proteins of Immunological Interest," National Institutes of Health; see also page 29, lines 15-20). Kabat et al. contains hundreds of immunoglobulin sequences representing immunoglobulins from a wide variety of mammals (human, mouse, rat, cow, pig, dog, goat sheep, etc.). The patent specification also contains structural information about immunoglobulin polypeptide domains, for both a heavy chain (page 29, 1-7) and a light chain (page 29, lines 21-27). Reference to structural information about abzymes also is found in the specification, for example, at page 30, lines 10-17. Further structural

information about immunoglobulins may also found in the examples in the patent application, as already noted by the examiner.

In addition to the ample structural and functional information about immunoglobulins contained in the instant application, one skilled in the art would also have known that there was a wealth of additional relevant information available in the public domain. The large scope of this information can be appreciated by the number of patents that have issued in the field of antibody engineering and by an even larger number of scientific publications in this art, the latter being readily evident from the background sections or the prior art sections of issued patents in antibody engineering (see background or prior art listings in, e.g., Carter et al. 6,054,297; Chou et al. 6,056,957; Queen et al. 5,693,762; Winter 5,225,539; and Huston 5,476,786). The passage from the background section in U.S. patent 6,054,297, which is shown below for the Examiner's convenience, is typical.

> The three-dimensional structure of immunoglobulin chains has been studied, and crystal structures for intact immunoglobulins, for a variety of immunoglobulin fragments, and for antibody-antigen complexes have been published (see e.g., Saul et al., Journal of Biological Chemistry 25:585-97 (1978); Sheriff et al., Proc. Natl. Acad. Sci. USA 84:8075-79 (1987); Segal et al., Proc. Natl. Acad. Sci. USA 71:4298-4302 (1974); Epp et al., Biochemistry 1 4(22):4943-4952 (1975); Marquart et al., J. Mol. Biol 141:369-391 (1980); Furey et al., J. Mol Biol. 167:661-692 (1983); Snow and Amzel, Protein: Structure, Function, and Genetics 1:267-279, Alan R. Liss, Inc. pubs. (1986); Chothia and Lesk, J. Mol Biol. 196:901-917 (1987); Chothia et al., Nature 342:877-883 (1989); Chothia et al., Science 233:755-58 (1986); Huber et al., Nature 264:415-420 (1976); Bruccoleri et al., Nature 335:564-568 (1988) and Nature 336:266 (1988); Sherman et al., Journal of Biological Chemistry 263:4064-4074 (1988); Amzel and Poljak, Ann Rev. Biochem. 48:961-67 (1979); Silverton et al., Proc. Natl. Acad. Sci. USA 74:5140-5144 (1977); and Gregory et al., Molecular Immunology 24:821-829 (1987). It is known that the function of an antibody is dependent on its three dimensional structure, and that amino acid substitutions can change the three-dimensional structure of an antibody, Snow and Amzel, supra. It has previously been shown that the antigen binding affinity of a humanized

> antibody can be increased by mutagenesis based upon molecular modeling (Riechmann, L. et al., Nature 332:323-327 (1988); Queen, C. et al., Proc. Natl. Acad. Sci. USA 86:10029-10033 (1989)).

Self evident from this quote is the vast amount of immunoglobulin structural information known before the earliest filing date of the instant patent application.

In view of the above, it is respectfully submitted that there was an established relationship between immunoglobulin sequence and structure by the earliest priority date of the instant application. Unlike the case in *Eli Lilly* where a single nucleotide sequence for insulin was found not to provide written description for a genus of insulin encoding sequences representing insulin from all mammals, there were hundreds of immunoglobulin nucleotide sequences representing immunoglobulin from a variety of mammals. In addition, there was extensive knowledge of immunoglobulin structure and function that was known at the earliest filing date. Thus, the basis allegedly supporting the instant rejection for written description is unfounded.

The existence of an adequate written description for the present claims is also consistent with the PTO's recently proposed "Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112(1) 'Written Description' Requirement" ("Revised Interim Guidelines"; 64 Fed. Reg. 71427, Dec. 21, 1999). The Revised Interim Guidelines state that determining whether an inventor is in possession of the claimed invention "is a conclusion reached by weighing many factual considerations, which "include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." As already discussed, extensive structural and functional information and correlation of structure with function was known about immunoglobulins. In addition, the level of skill in the art was high as indicated by the extensive publication history in antibody engineering, much of this knowledge being more than 20 years old. Finally, the patent specification contains an extensive description of how to make and use the claimed

invention. Thus, the factual considerations in the instant case clearly support that an adequate written description exists in the present case.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims for allegedly lacking written description.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The rejection of claims 53 has 55 for allegedly lacking clarity under 35 USC § 112, second paragraph is respectfully traversed. Claim 53 has been amended to recite "comprising," to make clear that the claim language is open.

Claim 55 has been rejected for allegedly lacking clarity with respect to the phrase "one-half an immunoglobulin molecule." It is respectfully submitted that one of ordinary skill in the art would understand this phrase to mean a molecule comprising a single heavy chain and a single light chain. This is based on the well-known understanding immunoglobulins are generally bivalent and that one half a molecule is a univalent immunoglobulin. However, in the interests of advancing prosecution, Applicant has amended claim 55 to specify that the immunoglobulin product comprises "one heavy chain and one light chain."

REJECTION UNDER 35 U.S.C. § 102 OVER DÜRING

The rejection of claims 53-56 and 58-63 under 35 U.S.C. § 102(b) as being allegedly anticipated by During (Dissertation) is respectfully traversed. Claim 66 has been cancelled herein, rendering the rejection moot as to this claim. All reference herein to the During dissertation are to the English language translation prepared by Ralph McElroy Translation Company, 910 West Avenue, Austin Texas (Job No. 1596-81522). The arguments below are supported by a declaration pursuant to 37 C.F.R. §1.132 by Richard Lerner, M.D., President of the Scripps Research Institute ("the Lerner declaration"), copy attached herewith.

At the outset, it is noted that the rejection is based on the belief that During has successfully demonstrated expression of an antibody in plant cells. As will be demonstrated below, the approach used by During is different and, in any event, the ordinary skilled artisan would not have believed During's assertions of success, and/or the During dissertation is non-enabling.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada F.2d, 15 USPQ2d 1655 (Fed. Clr, 1990), In re Bond, F.2d , 15 USPQ 1566 (Fed. Clr. 1990). Furthermore, it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d,1452, 221 USPQ 481 (Fed. Cir. 1984).

Argument

A. The claims are not anticipated (or obvious) because the During dissertation uses a different strategy from the claimed invention.

During fails to disclose or otherwise teach the elements of the claims including the requirement the light chain to have a leader sequence that forms a secretion signal which is cleaved following proteolytic processing and the requirement for an "antigen-specific" immunoglobulin product. The strategy used by During for expressing a two chain multimer (i.e., a light and heavy chain) differs from this claimed requirement. In the During dissertation, the nucleic acid encoding the barley alpha amylase signal sequence was inserted directly 5' to the end of the DNA encoding the amino terminal end of the mature heavy chain. In the case of the light chain, however, During included nucleic acid encoding three additional amino acids (Gly-Ser-Met) between the DNA encoding the leader sequence and the DNA encoding the mature amino terminus of the light chain. Lerner declaration, ¶9. The additional amino acids that would be encoded at the 3' end of the light chain leader sequence constructed by During were unusual, according to Lerner, and it was not clear what effect additional amino acids would have on final processing of the leader. Lerner declaration, ¶¶10 and 11. In is now clear from the art that mutations

introduced in the vicinity of a cleavage site have the potential to adversely influence signal processing. Lerner declaration, ¶11. In the opinion of Lerner, During's strategy of adding additional amino acids residues to the cleavage site for the light chain leader likely obscured substrate recognition causing cleavage site ambiguity. Lerner declaration, ¶¶11 and 12.

Thus, it is respectfully submitted that these facts alone evidence that the During dissertation does not teach the claimed requirement for proteolytic processing of a leader sequence for the light chain to form an antigen-specific immunoglobulin in the plant cell. It is respectfully submitted, therefore, that no substantive foundation exists upon which to find the claims anticipated (or obvious) over During and the rejection fails on this basis alone.

B. The claims are not anticipated (or obvious) because During's assertion of successful antibody expression in plants would not have been believed by the ordinary skilled artisan or, in the alternative, the During dissertation is non-enabling.

1. <u>There was a prejudice in the art against the possibility that plant cells could be used to produce an antigen-specific immunoglobulin</u>

Any analysis of the of the prior art in the context of an anticipation or obviousness rejection must be made from the perspective of the ordinary skilled artisan at the proper time frame. The Lerner declaration goes to great length to properly ascertain this perspective at the time period beginning from the alleged publication date of the During dissertation (July 1988) and up to the earliest filing date of the above captioned patent application (October 27, 1989). The analysis shows that there is strong evidence at the relevant time period for the existence of a prejudice in the art against the possibility of using plant cells to process and assemble an antigen-specific immunoglobulin. According to Lerner, it was appreciated by the early 1980s that the biology of antibody expression was complex and varied with the maturation state of the B cell. For example, rearrangement of immunoglobulin chain variable region encoding gene segments is

required to form a functional immunoglobulin gene, and rearrangement of the heavy chain occurs before rearrangement of the light chain. In fact, there is an early stage B cell known as the "pre-B cell," characterized in having a productively rearranged heavy chain V gene but not a rearranged light chain V gene. Lerner declaration, ¶3. In contrast, a later stage of B cells is known (i.e., "young B cell), characterized in having both the heavy and the light chain V genes productively rearranged and in expressing a full-sized immunoglobulin on the cell surface. *Id.*

Lerner goes on to explain that antibody expression in B cells was understood to be further complicated by the involvement of the BiP protein, known to be involved in heavy chain processing. Lerner declaration, ¶3. A phenomenon called heavy chain toxicity also was appreciated at the time but its mechanism was unknown. Lerner declaration, ¶4. According to Lerner, by the mid 1980s, a prejudice had taken hold in the art against the notion that antigen-specific immunoglobulins could be produced in cells other than mammalian B cells. *Id.*

Although Lerner notes the existence of reports describing expression of an assembled antibody in two microorganisms (i.e., *Saccharomyces cerevisiae* and *E. coli*) he provides substantial reasoning for why the prevailing prejudice in the art would still have existed with respect to producing antigen-specific immunoglobulin in plant cells. Lerner declaration, ¶7. For example, Lerner notes that plant cells were known to be different from mammalian cells and from microorganisms such as *Saccharomyces cerevisiae* and *E. coli* not only in having a cell wall but also in features related to protein secretion. In addition, Lerner notes that it was not known at the time whether plant cells contained a BiP protein or a functionally equivalent analogue. Lerner concludes from his review of the field that:

> [T]here was a sound basis for a real prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific around the time of the During dissertation (*circa* 1988/1989). Were this not the case, then Applicant's invention clearly would not have been roundly hailed in both the scientific literature and in the

> general press as a significant scientific discovery and medical breakthrough.

Lerner declaration, ¶8 (footnotes removed). It stands to reason, therefore, that the ordinary skilled artisan in the 1988/1989 time frame would have applied this prejudice to any claim purporting to demonstrate processing and assembly of an antigen-specific immunoglobulin in plant cells and would not have accepted such claim unless the proof was well founded. It is respectfully submitted that the teachings of the During declaration with respect to the rejection, must be viewed in light of this prejudice.

2. During's experimental results allegedly supporting immunoglobulin expression are internally inconsistent and are lacking in critical controls

During initially made a light chain only expression vector and evaluated whether plant cells transfected with this vector could express light chains. During, however, failed to detect light chain production in the cells (During dissertation, p. 80, line 2). According to Lerner, this fact would have been disturbing to the ordinary skilled artisan because light chain alone is readily expressed in B cells, and even if During's cells were making a small amount of light chain, albeit at a level below his detectability limit, this would complicate efforts to achieve and detect heavy-light chain assembly. Lerner further points out that an increased relative heavy chain expression, which under the circumstances might be necessary to obtain assembly in view of the low levels of expressed light chain, conceivably could result in toxicity if plant cells were susceptible to heavy chain toxicity, as was the case for mammalian B cells. These issues would have raised serious questions about During's chances for success and would have required additional proof for any alleged success to be accepted in the art.

Although During appreciated that his expression system was suboptimal, he proceeded to attempt expression of both a heavy and light chain from a single expression vector. Anticipating a threshold detectability problem, During utilized a pre-enrichment step prior to Western blotting (i.e., indirect Western) of transgenic plant extracts. Lerner declaration, ¶14. Lerner points out that During's need for an indirect Western also would

have been disturbing to the ordinary skilled artisan because direct Western blotting was known to be a very sensitive technique that had previously been successfully used to demonstrate foreign host expression (including plant expression of antibodies as disclosed in the instant patent application). *Id.*

The Examiner is referred to the Lerner declaration § 15 for details of During's indirect Western results. It is significant that During now observes light chain detection with the dual chain vector (but not with the light only vector used earlier) but was unable to detect heavy chains by either direct or indirect Western blotting. *Id.* During's assertion that he has detected the presence of assembled B1-8 antibody in the plant cells is based, according to Lerner, on faulty circular logic.

> To conclude as he does from the Western results that assembled B1-8 antibody was present in the plant extract, During must infer that which he is attempting to prove, that fully assembled antibody must have been present in the extract for light chain to have been enriched following binding to the NP hapten immunoabsorbent. As will be seen below, this faulty circular reasoning is open to alternative explanations that directly conflict with During's conclusion.

Lerner declaration, ¶ 15. Lerner goes on to discuss numerous other reasonable explanations for the results that During did not address, let alone attempt to exclude. Notably, During fails to exclude the real possibility that light chain may have been enriched by the NP immunoabsorbent even if the light chain were not assembled with a heavy chain. During's failure to detect heavy chains by direct and indirect Western blotting is consistent with this possibility. As summarized by Lerner, there was much that During could have done (but failed to do) to exclude alternative artifactual explanations for his Western blotting data.

> For example, During could have directly demonstrated that heavy chain was absolutely required for light chain binding during the pre-enrichment step. Alternatively, or in addition, During could have used biosynthetic radiolabeling of plant cells in combination with Western blotting to prove that a heavy chain was in fact co-enriched with light chain. This method is well known in the art and was previously used to demonstrate foreign protein expression. Biosynthetic radiolabeling also

> helps to control for stripping of antibody during a low pH elution of an antibody immunoabsorbent column (i.e., the Ls136 adsorbent), a problem encountered with CNBr. Since During employed low pH elution and CNBr linkage, he should have provided controls to address this potential problem.

Lerner declaration, ¶ 16 (footnotes removed).

The During dissertation also evaluated antibody expression in his plants using a second technique referred to as "tissue printing." In this technique, a leaf is pressed against a membrane in order to bind proteins in the leaf to the membrane, and the membrane is probed by immunological reagents as in Western blotting. The During dissertation describes that light chain, heavy chain and "aggregated B1-8" antibody were detected by tissue printing. Although During asserts that these results support his conclusion of successful immunoglobulin assembly, Lerner believes that the tissue printing experiment are just as readily subject to alternative explanations because they lack controls which are essential to conclude that binding of an immunological reagent is antigen-specific. Lerner declaration, ¶ 17. Lerner bases his belief not only on his own experience as a scientist and immunologist for more than 30 years but also on the scientific literature. With respect to the latter, Lerner points out that the types of controls lacking in the During dissertation were used by others who previous to During demonstrated expression in yeast of the same B1-8 antibody that During was attempting to express in a plant. *Id.* (referring to Wood et al.) The few controls used by During in the tissue printing experiments were wholly insufficient under the circumstances to support During's assertion of success.

The During dissertation also includes immunogold electron microscopic analysis of his transgenic plant cells apparently with the same antibodies used in the Western blotting and tissue printing experiments. The Examiner is referred to the Lerner declaration § 18 for a detailed explanation of During's immunogold results. Lerner takes issues with During's conclusion that the immunogold results indicate successful assembly of the B1-8 antibody in plants. First, Lerner notes that the heavy chain again was not detected. In addition, Lerner points out that the areas of the cell that were immunogold labeled with the light chain reagent were not the same areas that were immunogold labeled with the

Ac38 reagent (allegedly specific for an assembled B1-8 heavy and light chain). Lerner declaration, ¶ 18. It stands to reason that for assembly to have occurred, the two chains should be co-localized to at least one area of the cell. Furthermore, During failed to observe immunogold labeling in regions of the cell that one would normally have expected if antibody assembly were possible in plant cells. Lerner declaration, ¶ 19. Indeed, During observed immunoreactivity inexplicably in chloroplasts with the Ac38 antibody but not in the golgi apparatus or vesicles as others have observed previously for secreted proteins, including antibodies. Unusual results might be acceptable if plant cells were capable of antibody assembly in unique and previously unknown ways, however, unusual results cannot make up for the lack of controls in other experiments.

Lerner concludes that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed the assertion of the During dissertation that plant cells could be used to process and assemble an antigen-specific immunoglobulin. Lerner declaration, ¶ 22. Lerner bases this belief on During's failure to perform critical controls to support his conclusions and to explain his inconsistent results. Also, the Ac38 antibody which underlies virtually all of the support for During's assertion cannot be used, according to Lerner, to prove that NP antigen specific binding was present in transgenic plant cells. Lerner declaration, ¶ 22. Thus, even if During had done the proper antigen inhibition controls, more would have been needed, according to Lerner, to overcome the prejudice in the art. *Id.*

It is also Lerner's opinion that even if there were no prejudice in the art, During's conclusions would still not have been accepted. This view is based in part on Lerner's extensive experience as an editorial board member of more than ten scientific journals and an official reviewer for hundreds articles submitted for publication. Although During eventually published his antibody work in a peer-reviewed journal (i.e., 1990 article in "Plant Molecular Biology"), this occurred after the inventors of the above-captioned application published their work (1989 article in "Nature"). Furthermore, as noted by Lerner, During's publication discusses the earlier publication by the inventors Hiatt and Hein at some length, describing it as a successful demonstration of antibody expression in

plants. Lerner declaration, ¶ 22. In Lerner's opinion, had During not been able to support his work with the earlier publication by Hiatt and Hein, During's antibody expression experiments most likely would have been deemed unacceptable for publication. Lerner credits the inventors of the instant patent application, not During, as the first to convincingly demonstrate assembly of an antigen-specific immunoglobulin in plant cells.

As already described, During tried but failed to express a light chain polypeptide without the heavy chain and During made no attempt to express a heavy chain polypeptide without a light chain polypeptide. Thus, During does not disclose the requirement for nucleotide sequence to encode an immunoglobulin light chain polypeptide product. Applicant's position is supported by the Lerner declaration which credits expression of a antigen-specific single polypeptide immunoglobulin in plants to the instant inventors, not During.

> The During dissertation also fails to teach how to successfully use plant cells to express a heavy chain or light chain polypeptide, but not both, in plant cells. As already discussed, During attempted light chain expression without the heavy chain (but not vice versa) but failed to detect light chains in the plant cells. During did not even attempt to express heavy chains by themselves in plant cells. In contrast, the inventors of the above-captioned patent application, were the first describe that plant cells can express the light chain or the heavy chain separately in a plant cell. In my opinion, the ability of plants to express each individual chain (light or heavy) was unexpected, particularly in the case of the heavy chain which was known at least in mature B cells to cause toxicity when expressed without a light chain.

Lerner declaration, ¶ 25. On this basis alone, the During dissertation fails to anticipate claim 83 and its dependent claims.

Accordingly, because the During dissertation fails to disclose each and every element of the claimed invention, the claims are not anticipated under section 102(b) as a matter of law.

REJECTION UNDER 35 U.S.C. § 103 OVER DÜRING

The rejection of claims 53-66 under 35 U.S.C. § 103(a) as being allegedly obvious over During is respectfully traversed. Claim 66 has been cancelled herein, rendering the rejection moot as to this claim. The rejection is based on the belief that During has successfully demonstrated expression of an antibody in plant cells.

As has already been pointed out, the approach used by During is different and, in any event, the ordinary skilled artisan would not have believed During's assertions of success, and/or the During dissertation is non-enabling.

Relevant Law

A claimed invention is obvious if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103 (1994); see also Graham v. John Deere, 383 U.S. 1, 13 (1966).

Federal Circuit case law provides that "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." In re Dow Chem., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988). Under the law, there must be a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential evidentiary component of an obviousness holding." C.R. Bard, Inc. v. M3 Sys. Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed.Cir.1998). Also required is that the combined teachings have a reasonable expectation of success, viewed in light of the prior art. *See* In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988)("Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure.").

The examiner bears the burden of establishing a *prima facie* case of obviousness. In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed.Cir.1993); In re

Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed.Cir.1992). This showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not "evidence." *See* Dembiczak, 175 F.3d at 1000, 50 USPQ2d at 1617. However, the suggestion to combine need not be express and "may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Technology Corp., 121 F.3d 1461, 1472, 43 USPQ2d 1481, 1489 (Fed.Cir.1997). Only when the examiner's burden is met does the burden of coming forward with rebuttal argument or evidence shift to applicant. Rijckaert, 9 F.3d at 1532, 28 USPQ2d at 1956.

Argument

To reiterate, the claims require the light chain to have a leader sequence that forms a secretion signal which is cleaved following proteolytic processing and the requirement for an "antigen-specific" immunoglobulin product. As already discussed above, the Lerner declaration demonstrates that there was a prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific, around the time of the During dissertation (*circa* 1988/1989). It was further demonstrated that the During dissertation was so lacking in proof that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed During's assertion that plant cells could be used to process and assemble an antigen-specific immunoglobulin. It is respectfully submitted that difficulties and deficiencies of During would , if anything, have strengthened rather than weakened this prejudice. Even assuming arguendo that there was no such prejudice in the art, During's conclusions would still not have been accepted by the ordinary skilled artisan, according to Lerner, who bases his view on extensive experience as an editorial board member of more than ten scientific journals and an official reviewer for hundreds articles submitted for publication. During's eventual publication of his antibody work in a peer-reviewed journal (i.e., 1990 article in "Plant Molecular Biology"), occurred after publication by the inventors (1989 article in "Nature"), extensively discussed the instant inventors' successful prior work. In Lerner's opinion, this demonstrated that During's work was accepted for

publication only because it was supported by the earlier published success of the instant inventors, Hiatt and Hein. Lerner credits the inventors of the instant patent application, not During, as the first to convincingly demonstrate assembly of an antigen-specific immunoglobulin in plant cells.

Furthermore, as discussed, the During dissertation is wholly deficient with respect to teaching a plant comprising plant cells containing nucleic acid encoding an immunoglobulin light chain polypeptide product. During in fact teaches away from the claimed invention because During attempted **and failed** to express an immunoglobulin light chain polypeptide by itself and never attempted expression of the immunoglobulin heavy chain by itself. During dissertation translation, p.80, line 2. Even for what it purports to teach, as discussed above under the rejection for anticipation, the During dissertation would either not have been convincing or would have been considered a non-enabling disclosure. Thus, the teachings of the During dissertation would be even more deficient when considered in regards to a form of immunoglobulin that the reference does not even discuss.

It is respectfully submitted, therefore, that the above noted deficiencies in the teachings of the During dissertation demonstrate overwhelmingly that no substantive foundation exists upon which to find any of the claims obvious over this reference.

NON-STATUTORY DOUBLE PATENTING

Claims 53-66 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 6-12 of U.S. Patent No. 5,959,177;

Claims 53-66 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-7 of U.S. Patent No. 5,639,947; and

Claims 53-66 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-3 of U.S. Patent No. 5,202,422.

Applicants respectfully disagree and traverse the rejection. In the interests of furthering prosecution of the case, however, the above mentioned disclaimers are filed herein. Applicants reserve the right to later withdraw the disclaimer depending on circumstances.

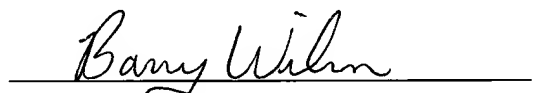
CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date: March 18, 2002

By 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

53. (Amended) A plant cell containing:

a) nucleotide sequence[s] encoding an antigen-specific immunoglobulin product [containing,] comprising at least a portion of the variable region of an immunoglobulin light chain and a leader sequence forming a secretion signal for said light chain, and;

(b) the antigen-specific immunoglobulin product encoded by said nucleotide sequences wherein said leader sequence is cleaved from said immunoglobulin light chain following proteolytic processing.

55. (Amended) The plant cell of claim 53 wherein the immunoglobulin product comprises [one-half an immunoglobulin molecule] one heavy chain and one light chain.

56. (Amended) The plant cell of claim 53 wherein the immunoglobulin product comprises [an] a full-length immunoglobulin light chain.

58. (Amended) The plant cell of claim 53 wherein the immunoglobulin product comprises [an] a Fab.

59. (Amended) The plant cell of claim 53 wherein the immunoglobulin product comprises [an] a Fab'.

60. (Amended) The plant cell of claim 53 wherein the immunoglobulin product comprises [an] a F(ab')2.

62. (Amended) The plant cell of claim 53 wherein the immunoglobulin product comprises [an] a full-sized antibody.

63. (Amended) The plant cell of claim 53 wherein the plant cell is from a dicotyledonous plant.

64. (Amended) The plant cell of claim 53 wherein the plant cell is from a monocotyledenous plant.

65. (Amended) The plant cell of claim 53 wherein the plant cell is from an alga.